REMARKS

Upon entry of the amendments, claims 1, 3, 5-9, 11-14, 20-22, 27, 54-56, 58-60, and 63-66 will be pending in the application. Claim 57 is cancelled, and claim 1 is amended. No new matter has been added.

Rejection under 35 USC 112, first paragraph

Claims 1, 3, 5-9, 11-14, 20-22, 27, and 54-62 are rejected for overbreadth and for lack of written description. Applicants note that claims 61 and 62 are cancelled. The rejections are traversed to the extent they are applied to the remaining claims as amended.

The Office contends in the paragraph bridging pages 3 and 4 of the Office Action that "[t]he claims as written encompass a broad genus of polypeptide with an unlimited number of possibilities with regard to the length of the polypeptide sequences. ...In addition, variation up to 15% of SEQ ID NO:1 (81^{15}) provide a range of activities, not all which are necessarily predictive of binding to leukocyte integrin."

Applicants respectfully disagree that a conclusion of non-enablement is warranted merely because the claim encompasses a large number of polypeptide sequences. Amended claim 1, from which claims 3, 11-14, 20-22, 27 and 54-59 depend, and claim 60 are directed to fusion peptides including a GPIIbα polypeptide that binds von Willebrand factor. Thus, a variant first polypeptide sequence that does not bind von Willebrand factor polypeptide is specifically excluded from the scope of the claims. Moreover, a conclusion of non-enablement is not warranted even if some polypeptide sequences are not enabled for other reasons. MPEP § 2164.08(b) states:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived,

> but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).

In addition, each component polypeptide for the claimed fusion proteins were known in the art. Human GPIbα polypeptide sequences, corresponding to SEQ ID NO:1 and SEQ ID NO:5 for the first claimed polypeptide are described in, e.g., Lopez et al., PNAS 84:5615-19, 1987 and Miura et al., J. Biol. Chem.175:7539-46, cited by the Office in rejections under 35 USC 103, below. Miura additionally describes methods for determining whether a GPIbα variant polypeptide binds to a von Willebrand factor polypeptide. Thus, both proteins were well-known in the art, as were methods of using these proteins.

The specification additionally provides a detailed explanation of the correlation between these functions and structural characteristics. Applicants explained in their previous response, the invention is claimed with reference to specific structural and functional requirements. For example, the specification at page 8, lines 5-32 provides extensive teachings of those regions and amino acid residues of GPIbα that bind with higher affinity to von Willebrand factor and which are important for protein stability. Thus, the specification correlates a claimed structure and function.

With these teachings in the specifications the artisan can readily determine that Applicants were in possession of the invention at the time of filing the application.

The specification also provides detailed, enabling teachings for making (pages 7-20) and using (pages 20-28) the claimed polypeptides. Methods for detecting binding of a GPIbα protein to a ligand such as those recited in claim 1 are also well known in the art

(see, e.g., Simon et al., J. Exp. Med. 192:193-204, 200, cited by Applicants at page 25, lines 30-32). Thus, one of ordinary skill in the art can readily practice the full scope of the invention now claimed using the teachings of the specification.

In view of the foregoing comments, Applicants request reconsideration and withdrawal of the rejection for lack of written description and enablement.

Rejections under 35 USC 103(a)

On the issue of obviousness, the M.P.E.P. § 2143.01 states "[e]ven when the combination of the references teaches every element of the claimed invention, but does not provide a motivation to combine, a rejection based on a *prima-facie* case of obviousness is improper." Furthermore, the case law is clear that "[t]he fact that a prior art device could be modified so as to produce the claimed device is not a basis for an obviousness rejection unless the prior art suggested the desirability of such a modification. *In re Gordon*, 733 F.3d 900, 221 USPQ 1125 (Fed. Cir. 1984). "To avoid the use of hindsight, courts have held that an invention is not obvious solely because it is composed of elements that are all individually found in the prior art. There must have been a suggestion in the art to make the combination and a reasonable expectation that the combination would be successful." *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988).

Applying the above standard to the present case, Applicants submit that none of the references cited by the Office, alone or in combination, suggest the desirability of the claimed invention. Absent such a suggestion, the claimed invention cannot be *prima facie* obvious even if every element of the claimed invention is found in the cited references.

Turning now to the first ground of rejection under 35 U.S.C. § 103(a), the Office asserts that claims 63 and 64 are obvious over Lopez et al., Proc. Nat. Acad. Sci. USA 84:5615-19, 1987 ("Lopez") in view of US Patent No. 6,277,975 ("the '975 Patent"). More specifically, the Office states:

> [O]ne of ordinary skill in the art at the time the invention was made would have been motivated to make a fusion protein using the GPIba region taught by Lopez et al. with the Fc portion of a human Iggg1 taught by the '975 patent because gpIba is a platelet receptor for von Willebrand factor which is required for adhesion of proteins during blood vessel injury and the Fc portion of native or mutated immunoglobulin sequences conferring desirable qualities such as longer half-life or reduced immunogenicity as taught by the '975 patent and the vWF binding domain of GpIba resides within the amino terminus of the molecule taught by Lopez et al.

Applicants respectfully submit that what the Office has considered as being motivation in this case is effectively hind-sight reconstruction of the claimed invention. Applicants do not dispute that Lopez identifies a vWF-binding domain of GPIbα, that binding of GPIbα to vWF is required for adhesion of proteins during blood vessel injury, and that the '975 patent reports that immunoglobulin sequences can increase in vivo half-life or reduce immunogenecity of fusion proteins containing these sequences. Applicants maintain, however, that Lopez lacks any suggestion of making a therapeutic agent that includes a vWF-binding region of a GPIbα protein. Moreover, because the alleged motivation for including immunoglobulin sequences stem from the advantages provided *in vivo*--i.e., increased half-life or reduced immunogenecity, the artisan would have had no motivation to combine Lopez with the '975 patent to arrive to the claimed invention.

As discussed previously, Lopez only discloses the amino acid sequence of the human wild type GPIbα polypeptide and fails to teach or suggest the claimed fusion proteins. The '975 patent, while disclosing fusion proteins having an Fc portion, does not

disclose or suggest any GPIbα polypeptides, let alone fusion proteins containing such polypeptides. Thus, because neither of these references provide any motivation to produce the claimed fusion protein, the rejection of claims 63 and 64 under 35 U.S.C. § 103(a) rejection should therefore be withdrawn.

Claims 1, 3, 6-9, 11-14, 21, 22, 27, and 54-60 are further rejected as being obvious over Miura et al. (J. Biol. Chem., 275:7539-46, 2000; hereinafter, "Miura") in view of the '975 patent. In applying this rejection, the Office asserts that it would have been obvious to substitute the calmodulin moiety in the GPIbα(G233V)-CaM and GPIbα(M239V) fusion proteins taught by Miura with the Fc portion of a human IgGγ1, as taught in the '975 patent, to arrive to the claimed invention. Applicants submit, however, that nowhere in the Miura disclosure or the '975 patent application is there any mention or suggestion of the desirability of such a substitution. Although the Office provides various reasons as to why such a substitution would be advantageous (e.g., increased half life and reduced immunogenicity), the cited references do not in themselves provide any motivation of the sort. Miura, as the Office contends, only goes so far as to state that "such a foundation could facilitate the development of antithrombotic agents that target the initial step of platelet adhesion." This statement, however, would hardly motivate one skilled in the art to modify the fusion protein of Miura to arrive to the claimed invention. Absent such a suggestion in the cited references, the claimed invention cannot be obvious <u>even if</u> every element of the claimed invention are found in the cited references. Accordingly, this aspect of the rejection should be withdrawn.

Claims 1, 3, 6-9, 11-14, 21, 22, 27, and 54-60 are further rejected as being obvious over US Patent No. 6,177,059 ("the '059 patent") in view of the '975 patent. In applying this rejection, the Office states that it would have been obvious to make the claimed fusion protein by substituting the lipid taught in the '059 patent with the Fc portion of a human IgGγ1 as taught by the '975 patent. Again, Applicants assert that, while the Office has provided various reasons as to the desirability of such a substitution (i.e. increased adhesion of GPIbα to Von Willibrand Factor, increased half life, and reduced immunogenicity), no such motivation is actually found in any of the two cited references, nor is there any expectation that any such substitution would be successful. Thus, this aspect of the rejection should be withdrawn.

Claims 1, 5, 20, and 63-66 are rejected as being obvious over Miura or the '059 patent in view of the '975 patent and further in view of US Patent No. 5,340,727 ("the '727 patent"). The Office asserts that it would have been obvious at the time of filing to insert the signal peptide taught in the '727 patent in the amino terminal end of the GPIbα polypeptide taught by Miura or the '059 patent and link the resulting polypeptide to the Fc portion of a human IgG1γ1, as taught in the '727 patent. Applicants assert that the '727 patent does not cure the deficiencies in the Miura reference, the '059 patent, and the '975 patent. In this regard, the '727 patent fails to provide any motivation for making the claimed fusion peptide. As is stated by the Office, the '727 patent teaches a GPIbα sequence containing a 16 amino acid signal peptide, which enhances cellular secretion of the GPIbα polypeptide. Nowhere does the '727 patent, however, mention or even suggest any fusion proteins and therefore, the '727 patent does not provide what is

missing in the other cited references. Thus, this aspect of the rejection may also be withdrawn.

In view of the foregoing reasons, Applicants respectfully request that the § 103(a) rejections be withdrawn.

Applicants submit that the application is in condition for allowance, and such action is respectfully requested. Should any questions or issues arise concerning the application, the Office is encouraged to contact the undersigned at the telephone number provided below.

A petition for extension of time accompanies this response. The Commissioner is authorized to charge payment of any additional fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 22058-503).

Respectfully submitted,

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